

# Positron Emission Tomographic Study of Post-Ischaemic-Hypoxic Amnesia

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## Key Words

Post-ischaemic-hypoxic amnesia · Positron emission tomography · Acetazolamide vasoreactivity · Frontal lobe dysfunction

## Abstract

**Background:** Despite extensive research, it still remains controversial as to what the precise location of the critical lesions underlying amnesia actually is. The amnesic syndrome is believed to be heterogeneous and due to several distinct functional deficits. **Patients and Methods:** Two patients, a 45-year-old woman and a 56-year-old man, with sudden cardiopulmonary arrest and successful resuscitation, were left with a clear amnesic syndrome as main neurological sequela. During their revalidation period, they underwent a positron emission tomographic (PET) examination, utilizing the <sup>13</sup>NH<sub>3</sub> bolus technique at rest and after intravenous acetazolamide administration. **Results:** Both PET studies showed more or less similar features with a decrease in regional cerebral blood flow (rCBF) in the frontal, temporal and parietal lobes. In addition, the rCBF was increased in both thalami of the 45-year-old woman and in the striata of the 56-year-old man. Acetazolamide vasoreactivity was most lost in the frontal lobes. **Conclusions:** In the present PET study, we demonstrated that destruction of the

inhibitory pathways to the thalamus and basal ganglia by ischaemic-hypoxic frontal lesions could be one of the mechanisms leading to amnesia.

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## Introduction

Organic amnesia is a syndrome in which preservation of intelligence and immediate memory are typically accompanied by various degrees of antegrade and retrograde amnesia. In general, amnesia may be caused by encoding, storage and retrieval deficits [1]. Despite extensive research it still remains controversial as to what the precise location of the critical lesions underlying amnesia actually is. Evidence is gradually accumulating that several distinct functional deficits underlie the syndrome [2].

If they exist, it is possible to isolate the responsible structures by using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). There are two main ways in which these procedures can be used: recording activity during the resting state in patients with known structural lesions and comparison with matched control subjects [3–5] or using memory challenge techniques in which the pattern of activation is compared between normal people and amnesics [6–8].

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MRI and PET studies in posthypoxic amnesia have revealed hypometabolism in the medial temporal lobes and hippocampi [9–12], but also in the limbic-diencephalic regions including the thalami [11–13], the caudate nucleus and the cerebellum [11].

The present report describes unusual PET findings in 2 patients with post-ischaemic-hypoxic amnesia.

## Patients and Methods

Two patients, a 45-year-old woman and a 56-year-old man, with sudden cardiopulmonary arrest and successful resuscitation, were left with a clear amnesic syndrome as main neurological sequela. During their revalidation period, 3 and 9 months after the acute event, respectively, they underwent a PET examination utilizing the  $^{13}\text{NH}_3$  bolus technique at rest and after intravenous acetazolamide administration. Although  $^{13}\text{NH}_3$  is an old PET tracer that reflects mainly capillary perfusion [14], it is also an indirect indicator of local cerebral metabolism [15] and it is suitable for assessing acetazolamide vasoreactivity in hypoperfused areas [16].

Both patients underwent a bedside cognitive evaluation on admission, using a brief mental status questionnaire (Jacobs test), adapted specifically to diagnose diffuse organic syndromes [17] and translated into Dutch. This test was validated by our local neuropsychological department [unpubl. data]. Subjects with scores of less than 20/30 were considered to have a significantly impaired cognitive capacity.

A full neuropsychological examination was performed in the first patient and attempted in the second at the time of the PET scan. The used mental status tests included the copying and subsequent reproduction from memory of the Rey-Osterrieth complex figure, Hooper visual organization test, Corsi block test, serial recitation test for numbers, Rey auditory verbal learning test, token test, assessing verbally mediated right-left discrimination and the Boston naming test.

Permission from the Hospital Ethics Committee was granted, and oral informed consent for the PET examination was obtained from the near relatives of the patients. A Neuro-Ecat IV scanner (EG&G/Ortec, Oak Ridge, Tenn., USA) with double rings of detectors and lateral and axial resolutions of 8.1 and 14.0 mm, respectively, was used. The distance between detector ring centres was 32 mm, and measurements were made in high-resolution mode using septa and shadow shields. After performing phantom scans with an external  $^{68}\text{Ge}/^{68}\text{Ga}$  ring source, the patient's head was positioned to accumulate data from transaxial planes centred 3 and 35 mm above the orbitomeatal line. A transmission scan was then performed using the same external source to correct subsequent emission scans for photon attenuation.

For measuring regional cerebral blood flow (rCBF), an intravenous bolus of 0.7 GBq  $^{13}\text{NH}_3$  was administered to the patients, and after 3 min, cephalic radioactivity was scanned for 300 s. As the half-life of  $^{13}\text{NH}_3$  is 10 min, a time interval of 25 min was respected before performing the consecutive PET examination. Acetazolamide at a dose of 22 mg/kg body weight was then administered intravenously, and after another 10 min, a similar bolus of 0.7 GBq  $^{13}\text{NH}_3$  was given with scan time starting after 3 min for 300 s. The high-dose acetazolamide was well tolerated by both patients.

Three slice reconstructions were obtained 3, 19 and 35 mm above the orbitomeatal line. Both patients had technically reliable measurements of the PET slices, including one through the basal frontal and temporal cortices and cerebellum, a second through the basal ganglia and thalami and a third at the level of the lateral ventricles. All PET planes could be superimposed on corresponding CT slices obtained around the time of the PET examination.

For each patient, ellipsoid regions of interest (ROIs) with axial axes of 30 mm and lateral axes of 15 mm (twice the camera resolution) were drawn over the cortical rim of the frontal, temporal, parietal and occipital lobes of both cerebral hemispheres. For the striata, thalami and cerebellar hemispheres circular ROIs, adapted to the size of the structures, were used. The cerebellum, both at rest and after acetazolamide administration, was used as reference region (100%).

The vasoreactivity was determined semiquantitatively in all ROIs taking normalized resting rCBF as 100%. The degree of acetazolamide reactivity was the percent difference between the number of counts in a particular ROI after administration of the drug against that at rest, using the same dose of  $^{13}\text{NH}_3$ . In our previous study, it was shown in a control group that the mean rCBF at rest increases on average with 36.6% ( $\pm 5.7$ ) in all regions after acetazolamide administration [16].

Kruskal-Wallis one-way analysis of variance and two-group Mann-Whitney U tests were used for statistical analysis. Statistical significance was set at p values less than 0.05.

## Results

### Case 1

A 45-year-old woman with a prior history of hypothyroidism and chronic alcohol abuse was transferred to the University Hospital following a cardiopulmonary arrest at home, probably due to myocardial infarction and ventricular fibrillation. After a successful reanimation and defibrillation by the resuscitation team, she was admitted in coma to the intensive-care unit. She needed artificial ventilation and was also treated with antibiotics for bronchopneumonia. She initially improved, but 24 days later she developed again an acute respiratory distress syndrome and had an episode of generalized tonic-clonic seizures, which was treated with phenytoin. She became afterwards alert and cooperative, and obeyed all commands. Initially she had an action myoclonus and a mixed positional and intentional tremor that disappeared after a few weeks. Except for a positive suck reflex, no other neurological deficits could be detected. She was transferred to the neurological department. The most remarkable finding was that, although she had fluent and normal speech, the verbal communication was inaccurate. She was disoriented in time and space and could not tell correctly about herself and her family. She confabulated and was euphoric. On a Jacobs test for cognitive function the score was 19/30. A CT scan of the brain revealed global cortical atrophy and moderate ventricular dilation without focal lesions.

A neuropsychological examination, 2.5 months after the acute event, revealed severe visuospatial dysfunction. There was an important attention deficit and copying was difficult but possible with perseverance. Encoding was difficult and explicit episodic memory was poor. Language understanding was good without aphasia. The examination concluded to a dysfunction of the frontal-limbic-reticular pathways more pronounced on the right side.

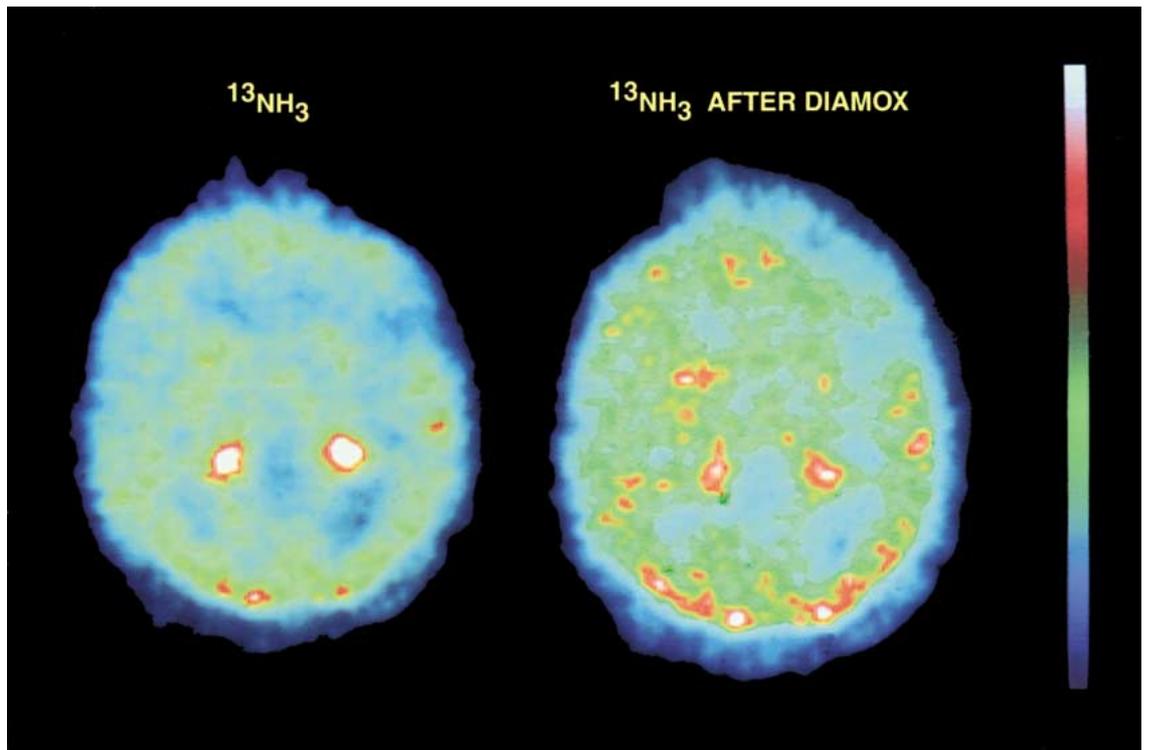
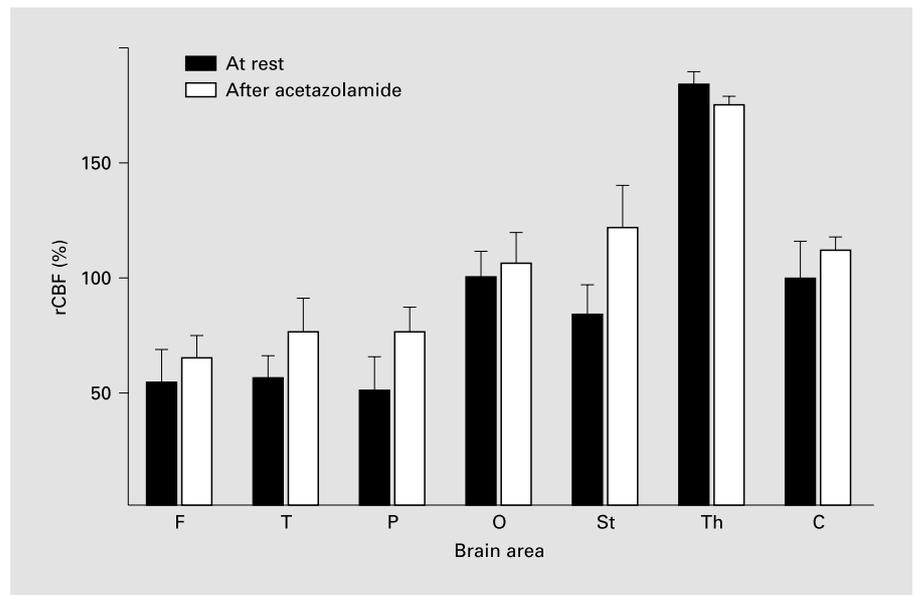


Fig. 1.  $^{13}\text{NH}_3$  PET slices of the brain at rest and after acetazolamide administration in case 1. The tracer uptake is high in both thalami and low in the anterior regions. After acetazolamide administration, rCBF is increased in all regions but less in the frontal lobes.

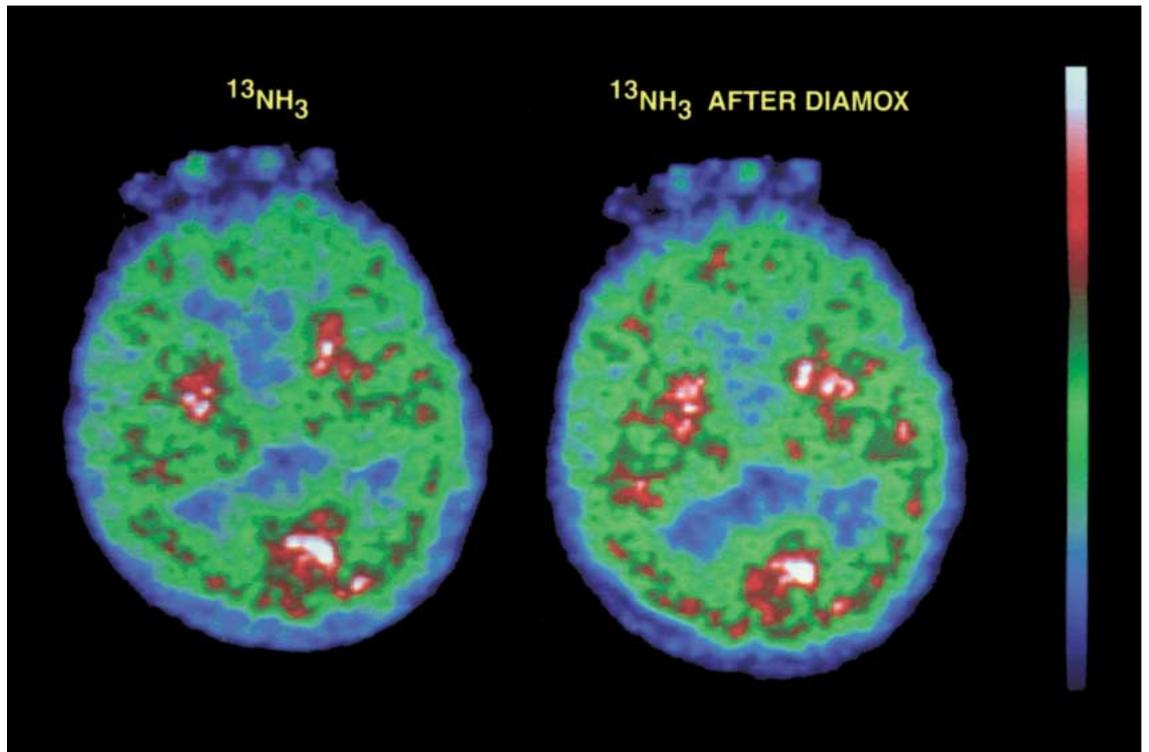
Fig. 2. Semiquantitative data of the tracer distribution in the frontal (F), temporal (T), parietal (P) and occipital (O) cortex and in the striatum (St), thalamus (Th) and cerebellum (C) at rest and after acetazolamide administration in case 1. rCBF is low in the frontal, temporal and parietal lobes and high in the thalami. Acetazolamide vasoreactivity is low in the frontal compared to the temporal and parietal lobes.



The PET examination was performed 3 months after the cardiac arrest. Visual analysis disclosed a high tracer activity in both thalami compared to the decreased activity in the frontotemporoparietal regions. After acetazolamide administration the  $^{13}\text{NH}_3$  activity increased in most regions but less in the frontal lobes. There were no significant asymmetries between both cerebral hemispheres (fig. 1). The semiquantitative data confirmed the decreased rCBF in the

frontal, temporal and parietal regions, compared to the cerebellum and the increased rCBF in the thalami (fig. 2). Acetazolamide vasoreactivity was less pronounced in the frontal lobes (18.4%) compared to the temporal (36.5%) and the parietal lobes (51.5%).

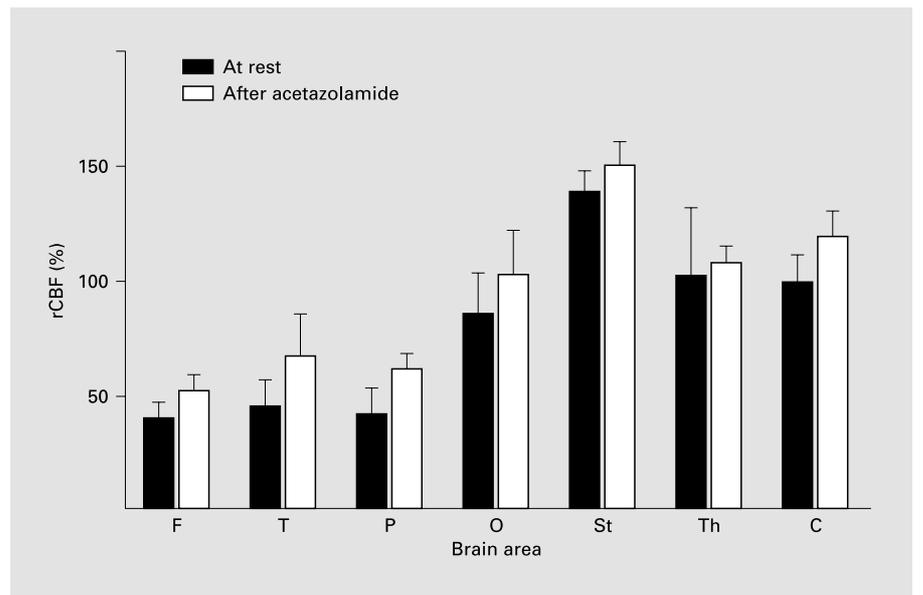
The mental status of the patient remained unchanged, and she was transferred to a chronic psychiatric department 1 month later.



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Fig. 3.  $^{13}\text{NH}_3$  PET slices of the brain at rest and after acetazolamide administration in case 2. The tracer uptake is high in both striata and low in the anterior regions. After acetazolamide administration, rCBF is increased in all regions but less in the frontal lobes.

Fig. 4. Semiquantitative data of the tracer distribution in the frontal (F), temporal (T), parietal (P) and occipital (O) cortex and in the striatum (St), thalamus (Th) and cerebellum (C) at rest and after acetazolamide administration in case 2. rCBF is low in the frontal, temporal and parietal lobes and high in the striatum. Acetazolamide vasoreactivity is low in the frontal compared to the temporal and parietal lobes.



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#### Case 2

A 56-year-old man with an unremarkable prior history was admitted to a peripheral hospital after a cardiopulmonary arrest due to myocardial infarction and ventricular fibrillation. The resuscitation had been arduous. The patient remained in deep coma for 48 h and needed artificial ventilation. His consciousness recovered slowly over a period of 7 weeks. He was discharged 1 week later. Due to

severe cognitive problems he was admitted to our neurological department 7 months after the acute event. The patient was confused and disoriented in time and space but could recognize his family. When alone, he was shouting and swearing. He could repeat numbers and words. He was able to make small calculations but on reading inverted the order of words. On a Jacobs test, he scored 7/30. He was incontinent and had a hesitating gait with small steps. There was a

moderate rigidity of arms and legs. Tendon reflexes were brisk without Babinski signs. Suck and grasp reflexes were present.

A full neuropsychological examination was not possible due to the extreme distraction of the patient.

CT scan and MRI of the brain showed severe cortical atrophy mainly of the anterior regions with enlarged ventricles. No focal lesions could be observed.

The clinical status remained unchanged. The PET examination, performed 9 months after the acute event, disclosed on visual analysis a high tracer activity in both striata compared to the decreased  $^{13}\text{NH}_3$  activity in the frontotemporoparietal regions. After acetazolamide administration, the  $^{13}\text{NH}_3$  activity increased in most regions but less in the frontal lobes. There were no significant asymmetries between both cerebral hemispheres (fig. 3). The semiquantitative data confirmed the decreased rCBF in the frontal, temporal and parietal lobes, compared to the cerebellum, and the increased rCBF in the striata (fig. 4). Acetazolamide vasoreactivity was less pronounced in the frontal lobes (28.3%), compared to the temporal (49.7%) and the parietal lobes (47.7%).

The patient was discharged home 3 months after his admission without any improvement.

## Discussion

In patients with sequelae of ischaemic-hypoxic encephalopathy after cardiopulmonary arrest and successful resuscitation the global decrease in blood flow and oxygen metabolism on PET scan correlates with the degree of brain damage and the clinical status of the patients [18].

The remarkable PET findings in our 2 patients with post-ischaemic-hypoxic amnesia are the preserved or possibly increased rCBF in the thalami in the first patient and in the striata in the second compared to the low rCBF in the cortical areas, supplied by the anterior circulation. As

the acetazolamide vasoreactivity is most disturbed in the frontal lobes, the memory deficits of both patients should be attributed mainly to structural damage of those regions.

Cardiopulmonary arrest can damage the brain by a lack of cerebral blood supply (ischaemic hypoxia) or by a lack of cerebral oxygen supply (anoxic hypoxia), although both mechanisms are likely to be involved to some degree. The main frontal involvement and the relative preservation of rCBF in the deep structures in our cases should suggest mainly an ischaemic-hypoxic cause rather than an anoxic one [19].

The frontal lobes are involved in encoding and retrieval. The right frontal lobe is activated during encoding and the left one during retrieval [20, 21]. Frontal lobe function is mediated through connections with temporal, parietal and associated visual-cortical areas [22] but also by frontal-subcortical circuits. The latter have in common a loop beginning in the frontal cortex, projecting to the caudate nucleus and putamen, in turn to the globus pallidus and substantia nigra, then to the thalamus and finally back to the frontal cortex [22]. In particular the dorsolateral frontal circuit is thought to be involved in attention span and working memory such as motor planning, deciding which stimuli to attend to and shifting cognitive sets [22–26]. The orbitofrontal circuit is heavily involved in emotional life and personality structure [27]. In both of our patients these frontosubcortical circuits must have been disturbed leading to loss of the inhibitory GABAergic processes [28] of the corticothalamic projections in the first patient and of the cortico-caudate projections in the second.

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